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NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE: Toxaphene **CAS REGISTRY NUMBER:** 8001-35-2

AMBIENT WATER QUALITY VALUE: 0.06 ug/L

BASIS: Oncogenic

I INTRODUCTION

The Ambient Water Quality Value applies to the water column and is designed to protect humans from the effects of contaminants in sources of drinking water; it is referred to as a Health (Water Source) or H(WS) value. Regulations (6 NYCRR 702.2) require that the water quality value be based on the procedures in sections 702.3 through 702.7. A previous fact sheet (NYS, 1985) supported a value for toxaphene of 0.01 ug/L based on oncogenic effects. Available information on toxaphene was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 0.06 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

Toxaphene has a Specific MCL of 3 ug/L as defined in 700.1. This is a maximum contaminant level for drinking water established by the New York State Department of Health under the State Sanitary Code (10 NYCRR Part 5, Public Water Supplies). Because toxaphene has a Specific MCL, determination of principal organic contaminant classes is not necessary.

The U.S. Environmental Protection Agency has established a maximum contaminant level goal (MCLG) of zero and a MCL of 3 ug/L for drinking water for toxaphene.

B. Derivation of Water Quality Value

Because toxaphene has a Specific MCL, a water quality value of 3 ug/L can be derived based on 702.3(a).

III ONCOGENIC EFFECTS (702.4)

A. Data

1. Pharmacokinetics

Ingested toxaphene concentrates in the liver then redistributes to fat (the principal storage tissue) over a longer period of time (Saleh et al., 1979). The oral administration of 10 mg/kg ^{14}C-toxaphene to rats resulted in residue levels of 6.4 ppm toxaphene and its metabolites in fat 7 days after exposure (Pollock and Kilgore, 1980). After two years exposure in a chronic dog study, toxaphene residues were measurable only in fat (Hercules Research Center, 1966).

Toxaphene is rapidly degraded in mammals following ingestion. The only metabolite identified in the urine, ^{36}Cl-chloride ion, of ^{36}Cl -toxaphene fed rats accounted for 50% of administered radioactivity (Oshawa et al., 1975). The percentage of a 20 mg/kg ^{36}Cl-toxaphene dose excreted over 9 days was 52.6%. Of this, 30% was in urine and 70% was in feces (Crowder and Dindahl, 1974).

2. Oncogenic Effects

Toxaphene is classified as B2, a probable human carcinogen by USEPA (1994). The International Agency for Research on Cancer classifies it in Group 2B, possibly carcinogenic to humans (IARC, 1987). However, both groups agree that toxaphene caused oncogenic effects in both rats and mice.

Two long-term carcinogenicity bioassays using toxaphene have been performed in rats and mice, with both species showing an oncogenic response. Toxaphene was administered in the diet to 54 B6C3F1 mice/sex/group for 78 weeks to give time-weighted average (TWA) doses of 0, 0.68, 1.9, and 4.8 mg/kg/day (0, 7, 20, 50 ppm) (Hart

et al., 1978). The animals were observed for 27 additional weeks. An increased incidence of hepatocellular carcinomas and adenomas was statistically significant in males exposed to 4.8 mg/kg/day. No treatment group of females differed significantly from controls although the incidence of tumors increased.

In the second study (NCI, 1979), dietary toxaphene was administered to 50 B6C3F1 mice/sex/group and 50 Osborne-Mendel rats/sex/group for 80 weeks. The animals were observed 11 weeks post-treatment. Mice of both sexes received TWA doses of 0, 11.3 and 22.6 mg/kg/day. Controls consisted of 10 matched controls/sex and 40 additional pooled controls/sex. A statistically significantly increased incidence of liver carcinomas and adenomas in treated mice was observed and was dose-related (NCI, 1979). Rats received TWA doses of 21 mg/kg/day and 42 mg/kg/day for males and 20 and 41 mg/kg/day for females. A statistically significant dose-related increased incidence of thyroid tumors (adenomas and carcinomas) was seen in both males and females (NCI, 1979).

3. Genotoxicity

Toxaphene causes mutations in bacteria (Mortelmans et al., 1986) and increases sister-chromatid exchange in human lymphoid cell line (Sobti et al., 1983). Metabolic activation is not required. Cells in lymphocyte cultures taken from toxaphene-exposed individuals have a higher incidence of chromosomal aberrations than cultures from individuals who have not been exposed (Samosh, 1974). These results lend support to the classification of toxaphene as an oncogen.

B. Derivation of Water Quality Value

1. Oncogenic Definition

The evidence of oncogenic activity in two mammalian species, rats and mice, after toxaphene exposure in the Hart et al. (1978) and NCI (1979) bioassays fulfills the definition of an oncogenic effect in 700.1(a)(24) for toxaphene.

2. Selection of Data

The results of the Hart et al. (1978) assay are selected as the appropriate dose-response data for deriving a value. This study showed oncogenic effects at a lower dose level than the NCI (1979)

study and used more dose levels. Moreover, overt toxicity was observed at the original concentrations in the NCI study and dietary levels were reduced one or two times. Effects seen at toxic doses near the maximum-tolerated dose may not be the same as effects at lower doses. U.S. EPA (1994) used the Hart et al. (1978) assay to derive an oral slope factor and a drinking water concentration of 0.03 ug/L at 10^{-6} risk. U.S. EPA (1991) also used the Hart et al. (1978) assay to derive a Great Lakes Initiative criterion for toxaphene. A summary of the data set showing statistically and biologically significant increases in tumor response for the most sensitive sex, strain and species is presented in Table I.

Table I

Male Mouse Tumor Response after Exposure to Toxaphene
Hart et al. (1978)

Sex/Species	TWA Dose* (mg/kg/d)	Tumor Type	Tumor Incidence
male mice	0	hepatocelluar carcinoma	10/53
	0.68		10/54
	1.9		12/53
	4.8		18/51

* Dose = ppm x .13 food consumption x 78 weeks exposure/105 weeks observed.

NYS (1985) derived a drinking water quality value based on the NCI (1979) bioassay dose-response data. On reevaluation, the results of the Hart et al. (1978) assay is the preferred dose-response data for the reasons cited above.

3. Model Selection and Output

6 NYCRR Part 702 specifies that values shall be calculated using valid dose-response data and a linearized multistage (LMS) low-dose extrapolation model unless scientific evidence is sufficient to support the use of another model. No data that would warrant the use of another model were found.

The low-dose extrapolation from experimental results to the risk level required by regulation (1×10^{-6}) was done with the GLOBAL82 LMS

model (CRUMP, 1982). The model derives both the 95% lower confidence limit (LCL) on the dose and the maximum likelihood estimate (MLE) of the dose. The MLE, when compared to the 95% LCL, provides a measure of goodness-of-fit of the data to the LMS model. There is a moderate difference between the 95% LCL estimate (0.012 ug/kg/day) and the MLE (0.12 ug/kg/day) of the dose corresponding to an extra cancer risk of 1×10^{-6} and a fair goodness-of-fit. This magnitude of difference, however, does occur relatively often. This reflects an inherent limitation of the LMS model to describe dose-response data that are initially flat but curve upwards at higher doses such as the data for liver tumors in mice in Table I.

The output of the model, i.e. the 95% LCL and MLE are shown in Table II. Part 702 specifies the 95% LCL as the basis of the water quality value.

Table II

GLOBAL82 Output - Hart et al. (1978)

		Animal Dose ug/kg/d	
Sex/Species	Tumor Site	95% LCL	MLE
male mice	liver	0.012	0.12

4. Calculation of Human Doses

The animal dose associated with a 1×10^{-6} excess cancer risk is converted as shown below to a human dose on the basis of the 3/4 power of relative body weights as proposed in Part 702. The weight of the male mouse is assumed to be 0.03 kg. The weight of an adult human is 70 kg.

$$\text{Human dose} = \left(\frac{\text{animal body weight}}{\text{human body weight}} \right)^{0.25} \times \text{animal dose}$$

$$\text{Human dose} = \left(\frac{0.03}{70} \right)^{0.25} \times 0.012 \text{ ug/kg/day} = 1.73 \times 10^{-3} \text{ ug/kg/day}$$

5. Selection of Human Dose and Discussion of Uncertainties

An adequate number of animals were exposed to an adequate number of doses to give an oncogenic response. The assay suffers from a less-than-lifetime exposure.

After toxaphene exposure, the most critical site in the male mouse is the liver. A human dose of 1.73×10^{-3} ug/kg/day associated with a risk of 10^{-6} was calculated as shown above from the male mouse data. The human dose based on the male mouse data is selected for calculation of the water quality value.

6. Calculation of Water Quality Value

The human dose associated with a 10^{-6} risk level is converted to a water quality value based on a 70 kg adult consuming 2 liters of water per day as follows:

$$\text{Water Quality Value} = \frac{(1.73 \times 10^{-3} \text{ ug/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.0606 \text{ ug/L},$$

rounded to 0.06 ug/L

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

Dogs given 4, 5 or 10 mg/kg/day toxaphene for 44 to 106 days showed degeneration of the renal tubular epithelium, accompanied by inflammation of the renal pelvis (Lackey, 1949). In a 13-week study in dogs, Chu et al. (1986) found renal and hepatic histopathological changes at 2 and 5 mg/kg/day and they identified a no-observed-adverse-effect-level (NOAEL) of 0.2 mg/kg/day.

Fitzhugh and Nelson (1951) observed increased liver weights with minimal liver cell enlargement in rats fed a diet for their lifetimes containing 25 ppm (approximately 1.25 mg/kg/day). Lehman (1952) reported no effects at 1.25 mg/kg/day, whereas 100 ppm (approximately 5 mg/kg/day) resulted in fatty degeneration of the liver. Boots Hercules Agrochemicals (not dated) reported liver necrosis in rats fed toxaphene at approximately 5 mg/kg/day for 3.7 years. In a 28-week, 2 litter rat study, Chu et al. (1988) found dose-dependent renal injuries in the proximal tubules of adult rats fed 20, 100 or 500 ppm toxaphene (calculated average intakes are: 1.8, 9 or 44 mg/kg/day) in their diet. Changes observed at 4 ppm (0.34 mg/kg/day) were not considered biologically significant by the authors compared to controls. No effects on reproductive performance or offspring were found.

1. Reproductive and Developmental Effects

Chernoff and Carver (1976) studied the potential fetal toxicity of toxaphene in CD rats administered toxaphene at doses of 15, 25 or 35 mg/kg/day in corn oil by gastric intubation on days 7 through 16 of gestation. At 35 mg/kg toxicity was shown by 31% maternal mortality. There was a dose-related reduction in weight gain of dams at 15 and 25 mg/kg/day. Despite maternal toxicity, there were no dose-related changes in fetal mortality or occurrence of fetal anomaly.

Allen et al. (1983) fed diets containing 0, 10, 100 and 200 ppm (1.3, 13, 26 mg/kg/day) toxaphene to breeding, pregnant and lactating female mice. Immunoglobin antibody titers were depressed in the dams and macrophage phagocytosis was suppressed in offspring. The lowest-observed-adverse-effect-level (LOAEL) for this effect is 1.3 mg/kg/day.

Olson et al. (1980) exposed pregnant rats from an unspecified time before birth and their pups from birth to 90 days after birth to 50 ug/kg/day toxaphene via the diet. All juvenile rats exposed to toxaphene showed significantly retarded maturation in a swimming test (days 10, 11, 12) and righting reflect test (days 14, 15), eventually attaining normal swimming ability. Tests of motivation, learning and retention on Days 70-90 showed no significant difference.

B. Derivation of Value

1. Selection of Data

The study by Chu et al. (1988) was judged appropriate for deriving a water quality value based on non-oncogenic effects. It was selected because it used several dose levels, an adequate number of animals/groups and reported dose-dependent effects. All other available studies (Fitzhugh and Nelson, 1951; Lackey, 1949; Chu, 1986; Allen et al. 1983; Chernoff and Carver, 1976; Crowder et al., 1980; Olson et al. 1980) either were much less-than-lifetime studies or used only one dose. Neither NCI (1979) or Hart et al. (1978) documented non-oncogenic effects other than weight changes and survival.

2. Calculation of Acceptable Daily Intake (ADI)

An ADI is calculated from the study of Chu et al. (1988) by dividing the NOAEL of 0.34 mg/kg/day by a total uncertainty factor of 1,000 as follows:

$$ADI = \left(\frac{0.34}{1000}\right) mg/kg/day = 0.35\ ug/kg/day$$

This uncertainty factor was selected to account for intra- and interspecies variation (10 x 10) and the use of a less-than-lifetime study (10).

3. Calculation of Non-oncogenic Water Quality Value

A water quality value is calculated from the ADI, above, based on a 70 kg adult consuming 2 liters of water per day and allocating 20% of the ADI to come from drinking water, as follows:

$$\text{Water Quality Value} = \frac{(0.34\ ug/kg/day)(70\ kg)(0.2)}{2\ L/day} = 2.4\ ug/L, \text{ rounded to } 2\ ug/L$$

Some rejected studies would yield more stringent values. All, however, are less stringent than the oncogenic value.

V CHEMICAL CORRELATION (702.7)

A value based on chemical correlation was not derived because values can be derived using NYCRR 702.4 and 702.5.

VI SELECTION OF VALUE

The H(WS) value is designed to protect humans from oncogenic and non-oncogenic effects from contaminants in sources of drinking water. To protect from these effects, regulations 6 NYCRR 702.2(b) require that the value be the most stringent of the values derived using the procedures found in sections 702.3 through 702.7. The oncogenic value of 0.06 ug/L (6 NYCRR 702.4) is the most stringent value derived by these procedures and is the ambient water quality value for toxaphene.

VII REFERENCES

ATSDR (Agency for Toxic Substance and Disease Registry). 1990. Toxicological Profile for Toxaphene. Washington, D.C.: U.S. Department of Health and Human Services.

Boots Hercules Agrochemicals. Not dated. Boots Hercules toxaphene insecticide summary of toxicological investigations. Bulletin T-105D (as cited in USEPA, 1986).

Chernoff, N. and Carver, B.D. 1976. Fetal toxicity of rats and mice. Bull. Environ. Contam. Toxicol. 15:660-664.

Chu, I., D.C. Villeneuve, C.W. Sun et al. 1986. Toxicity of toxaphene in the rat and beagle dog. Fund. Appl. Toxicol. 7:406-418. [As cited in ATSDR, 1990].

Chu, I., V. Secours, D.C. Vineneuve et al. 1988. Reproduction study in the rat. J. Env. Sci. Health B23(2):101-126.

Crowder, L.A., and E.F. Dindal. 1974. Fate of Chlorine-36-labeled toxaphene in rats. Bull. Environ. Contam. Toxicol. 12:320-327 (as cited in USEPA, 1987).

Crowder, L.A., G.C. Lanzaro, R.S. Whitson. 1980. Behavioral effects of methyl parathion and toxaphene exposure in rats. J. Environ. Sci. Health (B) 15:365-378.

Crump, K.S. 1982. GLOBAL82. Ruston, LA: K.S. Crump and Company, Inc.

Fitzhugh, O.G. and A.A. Nelson. 1951. Comparison of chronic effects produced in rats by several chlorinated hydrocarbon insecticides. Fed. Proc. 10:295.

Hart, E.R., R.P. Beliles, M. Sharer et al. 1978. Carcinogenic evaluation in mice: Toxaphene. Final Report. Prepared by Litton Bionetics, Inc. Kensington MD for Hercules, Inc. Wilmington, DE. LBI Project No. 20602.

Hercules Research Center. 1966. Toxaphene residue in dog tissues two-year feeding study - 1965. Current activity report. Wilmington, D.E. (as cited in ATSDR, 1990).

IARC (International Agency for Research on Cancer). 1987. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs vol. 1 to 42. Supplement 7 Lyon, France.

Lackey, R.W. 1949. Observations on the acute and chronic toxicity of toxaphene in the day. J. Ind. Hyg. Toxicol. 31:117-120.

Lehman, A.J. 1952. Oral toxicity of toxaphene. Quarterly Bulletin. Assoc. Food and Drug Office. 16:47.

Mortelmans, K., S. Haworth, T. Lawlor et al. 1986. Salmonella mutagenicity tests 2. Results from testing 270 chemicals. Environ. Mutag. 8 (Suppl 7): 1-119.

NCI (National Cancer Institute). 1979. Bioassay of Toxaphene for Possible Carcinogencity. Carcinogenesis Testing Program. Division of Cancer Causes and Prevention. National Institutes of Health. Bethesda MD: U.S. Department of Health, Education and Welfare. DHEW Pub. No. (NIH) 79-837.

6 NYCRR (New York State Codes, Rules and Regulations). Water Quality Regulations, Surface Water and Groundwater Classifications and Standards: Title 6 NYCRR, Chapter X, Parts 700-705. Albany, NY: New York State Department of Environmental Conservation.

10 NYCRR (New York State Codes, Rules and Regulations). Public Water Systems: Title 10 NYCRR, Chapter 1, State Sanitary Code, Subpart 5-1. Albany, NY: New York State Department of Health, Bureau of Water Supply Protection.

Olson, K.L., F. Matsumara, G.M. Boush. 1980. Behavioral effects on juvenile rats from perinatal exposure to low levels of toxaphene and its toxic components. Arch. Environ. Contam. Toxicol. 9:247-257.

Ohsawa, T., J.R. Knox, S. Khalifa et al. 1975. Metabolic dechlorination of toxaphene in rats. J. Agric. Food Chem. 23:98-106 (as cited in USEPA, 1987).

Pollock, G. A., and W. W. Kilgore. 1980. The excretion and storage of ^{14}C-toxaphene and two isolated ^{14}C-toxaphene fractions. J. Toxicol. Environ. Health 6:127-140 (as cited in ATSDR, 1990).

Saleh, M. A., R. J. Skinner, J .E. Casida. 1979. Comparative metabolism of 2,2,5-endo, 6-exo, 8, 9, 10-heptachlorobornane and toxaphene in 6 mammalian species and chickens. J. Agric. Food Chem. 27:731-737 (as cited in ATSDR, 1990).

Samosh, L.V. 1974. Chromosome aberrations and character of satellite associations after accidental exposure of the human body to polychlorocamphene. Cyto. Genet. 8:24-27 (as cited in ATSDR, 1990).

Sobti, R.C., A. Krishan, and J. Davies. 1983. Cytokinetic and cytogenetic effect of agricultural chemicals on human lymphoid cells in virto. II. Organochlorine pesticides. Arch. Toxicol. 52:221-31.

U.S. EPA (U.S. Environmental Protection Agency). 1987. Toxaphene Health Advisory. Office of Drinking Water. Washington, D.C.: U.S. Environmental Protection Agency.

U.S. EPA (Environmental Protection Agency). 1991. Great Lakes Initiative Human Health Criterion for Toxaphene; CAS No. 8001-35-2.

U.S. EPA (Environmental Protection Agency). IRIS (Integrated Risk Information System). 1994. Toxaphene on-line. Cincinnati, OH: Office of Research and Development and Environmental Criteria and Assessment Office.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd Edition. New York, NY: Van Nostrand Reinhold Company, Inc.

VIII SCOPE OF REVIEW

The widely-recognized sources listed below can often provide a comprehensive review of the toxicity of a substance and in some cases, the derivation of a value. These sources were searched for information on toxaphene and if found, examined. Where they were not found it is so noted.

- IRIS (U.S. EPA's Integrated Risk Information System) (on-line).
- RTECS (Registry of Toxic Effects of Chemical Substances) (on-line).
- CCRIS (Chemical Carcinogenesis Research Information System) (on-line).
- ATSDR (Agency for Toxic Substances and Disease Registry) toxicological profile.
- U.S. EPA ambient water quality criteria document.
- U.S. EPA health advisory.
- U.S. EPA drinking water criteria document.
- U.S. EPA Drinking Water Regulations and Health Advisories, Office of Water, May 1994.
- IARC (International Agency for Research on Cancer) Monographs Supplement 7.

The sources above are deemed adequate to assess the literature through 1989. Coverage of recent literature (through 1994) was provided by a New York State Library on-line search of the databases listed below.

- NTIS (National Technical Information Service)
- TOXLINE
- BIOSIS

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